Cost-effectiveness of boceprevir add-on treatment of hepatitis C virus genotype 1 patients in Denmark

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Publication date:
2013

Document Version
Early version, also known as pre-print

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PNI 78
ISPOR 16 th Annual
European Congress
November 2-6, 2013, Dublin, Ireland

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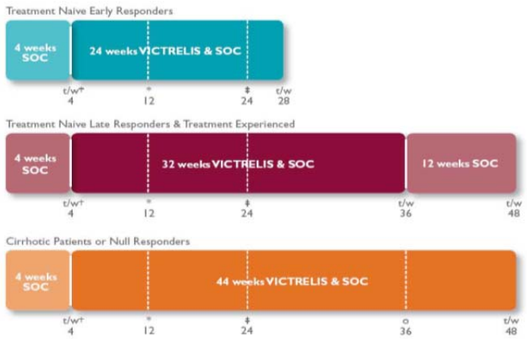
Background
Approximately 170 million people globally are infected by hepatitis C virus (HCV). In 2013, 17 000 patients were estimated to be HCV infected in Denmark. Only half of them have been diagnosed (1). HCV may cause liver cirrhosis and other liver-related complication such as hepatocellular carcinoma (HCC), which is the leading cause of liver transplants in the United States. (2, 3, 4, 5)
Of the six HCV genotypes, genotype 1 is the most common, but also the most difficult to eradicate by therapy (8, 9). In 2011, boceprevir (BOC), one of the first protease inhibitors, was approved for treatment of HCV genotype 1 infection in previously untreated and treated patients.

Objectives
The aim of this study was to evaluate the cost-effectiveness of boceprevir therapy in combination with pegylated interferon plus ribavirin (PEG+R), compared to PEG+R therapy alone, genotype 1 HCV patients, including treatment naïve as well as treatment experienced patients.

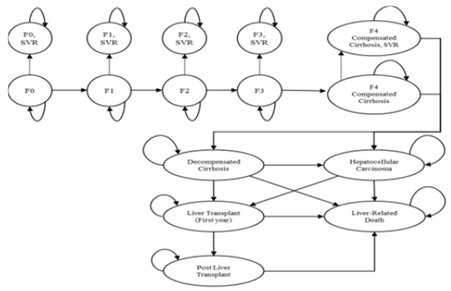
Methods
A Markov model simulating antiviral therapy and disease progression was developed to estimate lifetime healthcare costs and clinical outcomes of alternative treatment strategies. The model simulated the treatment regimens of dual therapy (PEG+R) and triple therapy (PEG+R+BOC), respectively, as recommended in the summary of product characteristics (SPC) and the Danish treatment guidelines. Data on clinical efficacy was taken from phase III clinical trials (SPRINT-2 and RESPOND-2).
The model projected the expected lifetime healthcare costs and clinical outcomes in quality-adjusted life years (QALY).
Costs were measured in 2012 Danish kroner (DKK) and clinical outcomes in (QALYs). Both costs and QALYs were discounted at 3 % per year.
Incremental cost-effectiveness ratio (ICER) was estimated for treatment naïve and experienced patients in comparison with PEG+R-based therapy.
Deterministic and probabilistic sensitivity analyses (PSA) on clinical inputs, costs, health state utility values, and sustained virologic response (SVR) rates were performed to assess the overall decision uncertainty.

Figure 1. Boceprevir treatment duration and futility rules as recommended by SpC



*futility rules: discontinue all three treatments if patients have HCV_RNA >= 100 IU/ml at week 12 of detectable viral load week 24. Viral load test week 4 (optional). Addition of boceprevir at start of week 5. For patients with cirrhosis (both treatment naïve and treatment experienced) and historical null responders recommended dosing: - 4 week PR lead in followed by 44 week tri-therapy with boceprevir PEG+ R.

Figure 2 Model Structure



Model inputs
All patient characteristics were based on information for the Danish database InfCare hepatitis database. (table 1). Treatment related parameters were estimated from SPRINT-2 and RESPOND-2. Information of the probability of receiving liver transplant was estimated from the Nordic liver transplant register (table 2). All health states and treatment related quality of life weights were obtained from previously published studies (table 3). Health state costs were based on previously published studies as well as DRG-tarifs (table 4).

Table 1 Patient characteristic (8)	Untrea	Treated
Gender (%)		
Male	73	73
Female	27	41
Mean age, years (SD)	50 (12)	52 (10)
Race (%)		
Caucasian	99	99
Black	1	1
Baseline METAVIR Score (%)		
F0	24	10
F1	43	27
F2	7	24
F3	6	13
F4	20	27

Table 2 Annual Transition probabilities	Baseline (range)
Fibrosis progression by use of Metavir score	
F0 to F1	0.117 (0.104–0.130)
F1 to F2	0.085 (0.075–0.096)
F2 to F3	0.120 (0.109–0.133)
F3 to F4	0.116 (0.104–0.129)
Cirrhosis progression	
Compensated cirrhosis to decompensated	0.029 (0.010–0.039)
Cirrhosis to HCC (5)	0.028 (0.010–0.079)
Decompensated cirrhosis to HCC (9)	0.068 (0.030–0.083)
Probability of Receiving a Liver Transplant	
Decompensated cirrhosis (10)	0.015 (0.010–0.062)
HCC (10)	0.006 (0-0.04)
Probability of moving from SVR to:	
Decompensated cirrhosis (10)	0.010 (0.002–0.036)
HCC (10)	0.006 (0.002–0.013)
Mortality Rates	
All-cause mortality (11)	age/gender specific
Liver-related mortality associated with	0.182 (0.065–0.190)
Liver-related mortality associated with	0.112 (0.065–0.190)
Liver-related mortality associated with HCC	0.427 (0.330–0.860)
Liver transplant (first year)	0.116 (0.060–0.420)
Liver transplant (subsequent years)	0.044 (0.024–0.110)

Table 3. Utility Weights	Baseline (range)
Baseline utility weights for general	
Anti-viral drug therapy-related	
Peginterferon + ribavirin, no side	0.85 * (baseline fibrosis-stage utility)
Peginterferon + ribavirin +	0.85 * (baseline fibrosis-stage utility)
Anti-Viral-related anemia	(0.83*0.85)*(baseline fibrosis-stage
Post treatment	
Sustained virologic response (cured)	0.83 (0.77–0.90)
Health state utility weights	
F0	0.76 (0.68–0.83)
F1 (14)	0.76 (0.68–0.83)
F2 (14)	0.76 (0.68–0.83)
F3 (14)	0.76 (0.68–0.83)
Compensated cirrhosis	0.74 (0.66–0.83)
Decompensated cirrhosis (first year)	0.66 (0.46–0.86)
Decompensated cirrhosis	0.66 (0.46–0.86)
Hepatocellular carcinoma	0.65 (0.44–0.86)
Liver transplant (first year)	0.69 (0.62–0.77)
Liver transplant (subsequent years)	0.69 (0.62–0.77)
Discount rate	3%

Table 4 Economic Inputs (DKK)	Baseline
Anti-viral drug therapy-related costs (weekly)	
Ribavirin + Peginterferon (15)	2 002
Boceprevir (15)	6 078
Erythroprotein (to treat anemia)	0
Monitoring Costs [1]	239
Health state costs (annual)	
F0 (16)	2 850
F1(16)	2 850
F2 (16)	2 850
F3 (16)	2 850
Compensated cirrhosis (17)	13 600
Decompensated cirrhosis (first year) (17)	47 050
Decompensated cirrhosis (subsequent years) (17)	47 050
Hepatocellular carcinoma (first year) (17)	62 040
Hepatocellular carcinoma (subsequent years) (17)	2 850
Liver transplant (first year) (17)	865 253
Liver transplant (subsequent years) (17)	61 306
Discount Rate for future costs(17)	3%
Time Horizon	Lifetime

Results
The ICER for PEG+R+BOC therapy versus standard therapy with PEG+R was DKK 241,774 for treatment naïve HCV patients and DKK 98,371 for treatment experienced patients. PSA for treatment naïve patients showed a probability of cost-effectiveness of PEG+R+BOC therapy compared to PEG+R of more than 65 % at a willingness-to-pay threshold of DKK 300,000 (approx. £30,000).

Table 5 Result			
Treatment naive	Incremental costs	Incremental QALY	ICER's DKK
Overall BOC vs Peg/R	123,614	0.51	242,380
F0-F3 BOC vs PEG/R	109,493	0.62	176,602
F4 BOC vs PEG/R	181,225	0.1	1,812,250
Treatment experienced			
Overall BOC vs Peg/R	133,271	1.36	97,993
F0-F3 BOC vs PEG/R	131,333	0.86	152,713
F4 BOC vs PEG/R	138,638	2.72	50,970
NR BOC vs PEG/R	145,623	0.87	167,383

Figure 3 Results of PSA for tr eatment naive

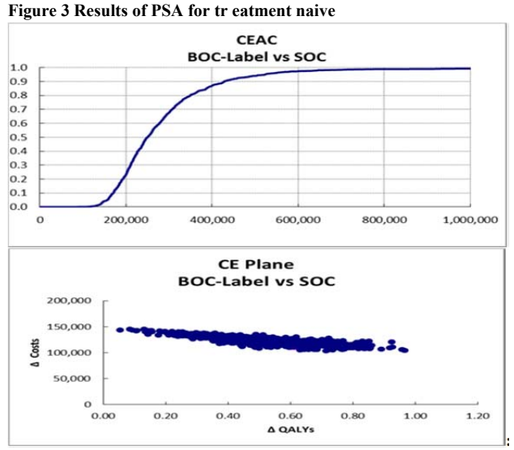
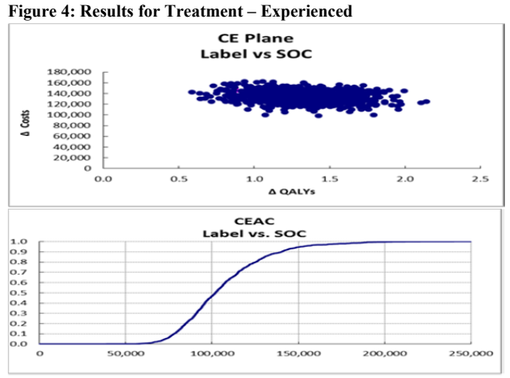


Figure 4: Results for Treatment – Experienced



Conclusions
From a Danish health economical perspective PEG+R+BOC therapy is cost effective in HCV genotype 1 patients to eradicate virus and to prevent development of late liver manifestations, such as cirrhosis and hepatocellular carcinoma (HCC) irrespectively of previous treatment status.
The result was robust to changes in the model as demonstrated by the sensitivity analyses.

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